

The impact of early morning off in Parkinson's disease on patient quality of life and caregiver burden



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ABSTRACT

Background: Early morning off (EMO) is a symptom experienced by patients with Parkinson's disease (PD) in any stage of the illness; however, few studies have explored its prevalence. Thus, the impact of EMO on patient Quality of Life (QOL) and caregiver burden is unclear.

Materials and methods: A QOL questionnaire was administered to members of the Japan Parkinson's Disease Association and their caregivers via mail using the PD questionnaire – 8 (PDQ-8), which measures the appearance of EMO. The analysis assessed the responses from 2205 completed surveys.

Results: Patients who felt they had EMO amounted to 79.8%, with 37.8% of respondents stating that EMO was a daily occurrence. The prevalence of EMO increased as the Hoehn and Yahr stage increased, but was observed at a rate of 52.4% even in patients at Stage 1. The QOL of those with EMO was significantly reduced ($p < 0.0001$), and the odds of caregivers feeling a sense of burden was higher for the group that experienced EMO even after adjusting for age of patient, age of caregivers, disease duration, relationship to patient, and Hoehn and Yahr stage.

Conclusion: The prevalence of EMO in the survey results was high, significantly lowering the patients' QOL. Interestingly, EMO was also observed in the early stage of the disease. Since the presence of EMO impacts patients' QOL and caregiver burden, medical intervention and appropriate gathering of information for such intervention should be considered.

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1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, next to Alzheimer-type dementia in the elderly population, and in Japan, approximately 141,000 people have been reported to have PD [1]. It is anticipated that the number of patients will further increase as the Japanese population continues to age rapidly. Recent advances have been made in pharmacotherapy for patients with PD such as dopaminergic medications. Because improvements in the accuracy of PD diagnosis and treatment have led to the life expectancy in patients with PD being nearly identical to those of healthy individuals, improvement of the quality of life (QOL) is now an important issue while planning treatment [2]. It is important to ask individual patients about their anxieties and concerns and have them choose appropriate treatments because PD is a disease that requires long-term care. Moreover, in most patients with PD, care becomes necessary in advanced stages. In such patients with PD, care giving turns into a long-term issue, and the reduction of caregiver burden is a challenge that should be considered concurrently with treatment for patients. In the previous

questionnaire survey that was conducted on patients with PD, we found that approximately 70% of patients experienced periods of time of insufficient drug efficacy with reduction in QOL, and that more than half of patients in this group were aware of the insufficient drug efficacy both during the night and early morning [3]. Inappropriate pharmacotherapy or insufficient management of wearing-off can frequently lead to early morning off (EMO). There have been long-acting dopamine agonists that have been available to control symptoms during these nighttime and early-morning periods. Hence, such agonists have garnered attention in recent years, as it has become possible to cope with nighttime symptoms to a certain degree. Thus, an investigation regarding the impact of EMO on patient QOL and caregiver burden was conducted.

2. Materials and methods

A countrywide survey was conducted by mail among 8001 members of the Japan Parkinson's Disease Association. This study was conducted upon receiving the approval of the Fukuoka University Hospital's Ethics Committee. When the patient returned the questionnaire, it was taken as consent to use the patient's data. Two types of questionnaires (one for patients and one for caregivers) were sent to the members' addresses, and the questionnaires were returned in the mail after they had been completed. The survey was conducted from August 13

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Table 1
Demographics of patients and caregivers. Data are presented as n (%) unless stated otherwise.

	Total sample				Patient and caregiver dyads			
	Patients n = 2632		Caregivers n = 2206		Patients n = 2155		Caregivers n = 2155	
Age (mean, sd)	70.7	(7.9)	67.7	(10.7)	70.9	(7.6)	67.7	(10.7)
Gender								
Male	1100	(41.8)	967	(43.8)	963	(44.7)	946	(43.9)
Female	1424	(54.1)	1137	(51.5)	1103	(51.2)	1109	(51.5)
Employment								
Employed	186	(7.1)	619	(28.1)	144	(6.7)	603	(28.0)
Help with housework	288	(10.9)	64	(2.9)	238	(11.0)	63	(2.9)
Unemployed	2095	(79.6)	1324	(60.0)	1721	(79.9)	1296	(60.1)
Hoehn and Yahr stage								
Stage I	76	(2.9)	–		48	(2.2)	–	
Stage II	207	(7.9)	–		169	(7.8)	–	
Stage III	959	(36.4)	–		785	(36.4)	–	
Stage IV	322	(12.2)	–		282	(13.1)	–	
Stage V	92	(3.5)	–		86	(4.0)	–	
Time since first diagnosis								
<3 years	221	(8.4)	–		156	(7.2)	–	
3–7 years	681	(25.9)	–		533	(24.7)	–	
More than 7 years	1675	(63.6)	–		1419	(65.8)	–	
Parkinsonian medication(multiple answer)								
Levodopa	1667	(63.3)	–		1355	(62.9)	–	
Pramipexole IR	1076	(40.9)	–		875	(40.6)	–	
Pramipexole ER	215	(8.2)	–		173	(8.0)	–	
Ropinirole	474	(18.0)	–		383	(17.8)	–	
Cabergoline	294	(11.2)	–		246	(11.4)	–	
Pergolide	294	(11.2)	–		245	(11.4)	–	
Bromocriptine	58	(2.2)	–		49	(2.3)	–	
Entacapone	945	(35.9)	–		790	(36.7)	–	
Selegiline	918	(34.9)	–		763	(35.4)	–	
Zonisamide	460	(17.5)	–		380	(17.6)	–	
Living in same household								
Yes	–		1967	(89.2)	–		1927	(89.4)
Relationship to patient								
Spouse	–		1753	(79.5)	–		1717	(79.7)
Child	–		214	(9.7)	–		205	(9.5)
Parent	–		92	(4.2)	–		91	(4.2)
Other family member	–		13	(0.6)	–		12	(0.6)
Others	–		31	(1.4)	–		29	(1.3)

through October 10, 2012. The questions in the survey included age, gender, work situation, Hoehn and Yahr stages [4], disease duration from the onset, pharmaceuticals used, QOL (Parkinson's disease questionnaire-8: PDQ-8) [5,6], whether they had experienced EMO, frequency of EMO (days/week), and problems due to EMO. The questions in the survey for caregivers included age, gender, work situation, whether they were living with the patient, relationship to the patient, sense of burden for giving care (independent questionnaire listed below), whether their patient had experienced EMO, frequency of EMO (days/week), and problems due to EMO.

The possible responses regarding the sense of burden for giving care were as follows: never, once in a while, sometimes, frequently, and always. The individual questionnaire asked caregivers to respond to the following issues:

1. Cannot go out
2. Feeling the responsibility of needing to provide care and experiencing anxiety
3. Feeling depressed
4. Feeling easily fatigued
5. Being unable to concentrate on work or hobbies and pleasure
6. Feeling anxiety about life in the future
7. Unable to have enough time for yourself
8. Feeling like care giving is worsening your physical condition.

The patients who answered “yes” to the question of “do you feel like your bodily movements are poor when you wake up?” were defined as having EMO. The caregivers who answered “yes” to the question of “do you feel like the bodily movements of the family member with PD are poor when they wake up?” were defined as having experienced EMO.

The PDQ-8 calculates the respondents' PDQ-8 summary index (PDQ-8-SI). The descriptive statistics were determined by whether the symptoms were present when waking up. Student *t*-test was used to compare the average values of the PDQ-8-SI. Caregiver burden was categorized as being “present” if the caregiver answered “sometimes”, “frequently”, or “always”, and categorized as “not present” if the caregiver answered “never” or “once in a while.” Then, the descriptive statistics were derived by category for each of the question items. Fisher's exact test was used to examine the association between the treatment type and the prevalence of EMO. The univariate logistic regression analysis was used to investigate the influence of the absence or presence of EMO and the level of severity on the Hoehn and Yahr scale (stage III or higher, or stage II or lower) on caregiver burden. Furthermore, the following variables were adjusted in the multivariate logistic regression analysis for EMO as a confounding factor: age of patient, age of caregivers, time since first diagnosis, relationship to patient, and Hoehn and Yahr stage. The significance level for all of these analyses was taken to be 5% for both sides. Statistical analyses were performed with SPSS version 22.0 for Windows (IBM Japan, Tokyo, Japan).

3. Results

Responses were received from 2632 patients with PD and 2206 caregivers during the survey period and there were 2155 cases where responses were received from both patient and caregiver. The backgrounds of patients and caregivers are shown in Table 1 (Data excluding persons with missing data on each questionnaire). The average patient age was 70.7 ± 7.9 years, and 54.1% of patients were women. In terms of the Hoehn and Yahr scale, stage III was the most prevalent at

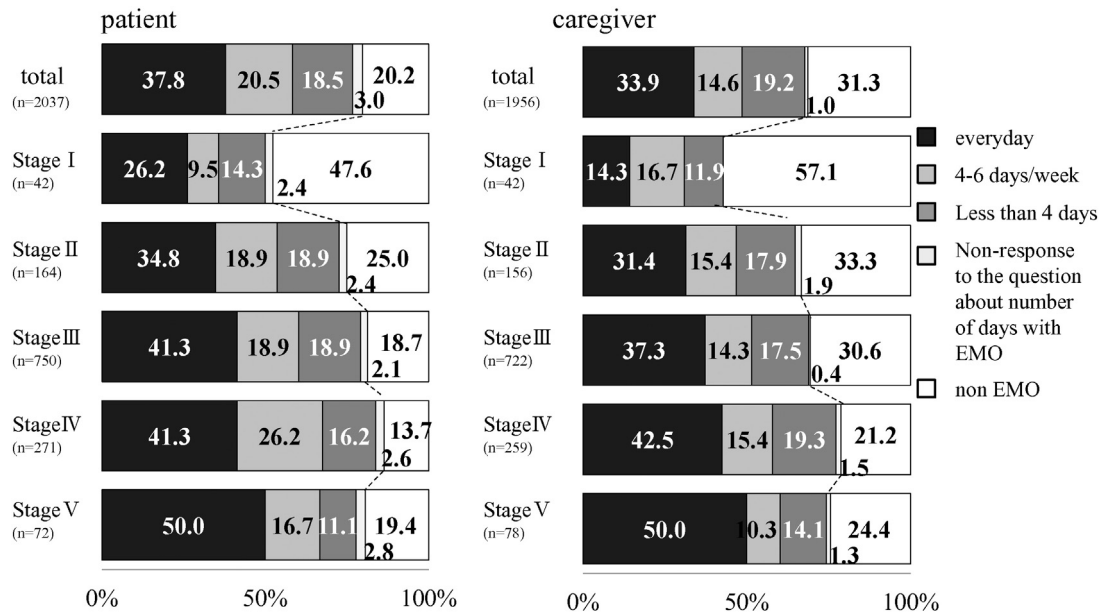


Fig. 1. Prevalence of early morning off (EMO). The frequency of EMO in patients with Parkinson's disease is shown according to the classification on the Hoehn and Yahr scale of severity. There is an astonishing level of common awareness demonstrated between patients and caregivers. Moreover, it should be noted that there is an unexpectedly high frequency of EMO in non-severe stage I and II patients. One of the causes of this is believed to be insufficient treatment.

36.4%, followed by stage IV at 12.2%. The most frequent response for the amount of time with the illness was 7 or more years with a response rate of 63.6%. The average age of the caregivers was 67.7 ± 10.7 years. Caregivers were 51.5% women, and their family relationship with the person with PD was 79.5% spouses, 9.7% parents, and 4.2% children. A significant number (89.2%) of these caregivers lived together with the patient.

EMO was observed in 79.8% of all patients, and 52.4% of patients were at Stage I on the Hoehn and Yahr scale. The percentage of caregivers who responded that they had experienced EMO was 68.7% and this was around 10% lower than patients who responded that they had EMO (Fig. 1). Among those reporting that EMO occurred daily, 37.8% were patients and 33.9% were caregivers. Among those under Stage I on the Hoehn and Yahr scale, 26.2% of patients, and 14.3% of their caregivers responded that they experienced EMO every day. Among the respondents who answered that they had EMO, the troubles caused by EMO for patients were “difficulties changing clothes” 68.0%, “difficulties using the bathroom” 44.2%, “being unable to be active in the morning” 42.9%, “difficulties having meals” 35.0%, “being a nuisance to the family” 31.2%, and “waking up with pain” 17.3%. The troubles caused by EMO for caregivers were “assisting in changing clothes” 47.0%, “assistance with the bathroom” 28.8%, “being unable to be active in the morning” 27.5%, “being unable to go out” 26.7%, “providing

assistance with meals” 26.0%, and “providing assistance with taking medicine” 19.4%.

The PDQ-8-SI score for the group with EMO was 42.3 ± 20.2 , while the score for the group without EMO was 30.7 ± 20.1 . Thus, a comparison shows that the PDQ-8-SI score for the group with EMO was significantly higher than that of the group without EMO (Table 2). According to the Hoehn and Yahr stages, the group with EMO had a significantly worse QOL for people in stages I–IV. The questions on caregiver burden that had the highest percentages were “feeling anxiety about life in the future” 57.0%, “feeling the responsibility of needing to provide care and experiencing anxiety” 50.5%, and “being unable to have enough time for one's self” 46.8%. When the odds were calculated for the influence of EMO on caregiver burden, the caregiver burden was increased for all of the items in the group with EMO. To remove the influence of age of patient, age of caregivers, disease duration, relationship to patient, and Hoehn and Yahr stage on caregiver burden, multivariate logistic regression analysis was used and the adjusted odds ratio was calculated (Table 3). Thus, EMO has independent impact on all the caregiver burden parameters.

4. Discussion

This survey clarified the real conditions of EMO for patients with PD and the burden on caregivers that it causes. EMO was observed in approximately 80% of patients. It should be noted that approximately 50% of patients under stage I on the Hoehn and Yahr stage experienced EMO, and as the level of severity increased, the percentage of patients with EMO increased. The frequency of EMO did not depend on the level of severity, and approximately half of patients with EMO answered that they experienced it every day. Thus, our survey showed that EMO occurs with a high degree of frequency. There has been little research focusing on EMO; however, according to a report by Chapuis et al., early-morning akinesia was observed with a frequency of 58.5% [7]. In the ongoing observational study being conducted by Rizos et al., it has been observed at a frequency of 61.0% [8]. Moreover, Rizos et al. are conducting an examination of EMO according to the level of severity of PD. This study reports that EMO occurs at a rate of 47.7% for mild cases (Stage 1–2.5 on the Hoehn and Yahr scale), 68.8% for moderate cases (Stage 2.5–3 on the Hoehn and Yahr scale), and 61.8% for severe cases (Stage 4–5 on the Hoehn and Yahr scale) [8]. While there are

Table 2
Comparison of PDQ-8-Summary Index between patient groups with and without EMO.

	Total		Patients with EMO		Patients without EMO		p value*
	n	PDQ-8-SI	n	PDQ-8-SI	n	PDQ-8-SI	
Total	1976	40.0 ± 20.9	1496	42.3 ± 20.2	387	30.7 ± 20.1	<0.0001
Hoehn &Yahr stages							
Stage I	47	25.7 ± 18.7	22	33.1 ± 16.6	20	16.7 ± 18.6	0.0044
Stage II	156	34.4 ± 19.9	114	39.0 ± 19.3	40	22.7 ± 16.4	<0.0001
Stage III	740	37.4 ± 17.8	577	38.9 ± 17.8	131	31.7 ± 15.9	<0.0001
Stage IV	264	49.1 ± 19.3	221	50.4 ± 19.4	35	39.4 ± 16.3	0.0017
Stage V	72	66.2 ± 23.4	48	67.1 ± 20.7	13	57.2 ± 32.4	0.1828

Data excluding 178 patients without response on PDQ-8-Summary Index and 93 patients without response on experienced EMO. Data are expressed as numbers of patients, mean ± SD, or p values.

* Student t-test (comparison between the two groups).

Table 3
Caregiver burden and its relation to PD severity of the patient and presence of EOM.

Dependent variables	Severity of PD (vs. <3 H&Y)			With EMO (vs. without EMO)					
	Univariate			Univariate			Multivariate ^a		
	OR	95%CI	p-Value	OR	95%CI	p-Value	OR	95%CI	p-Value
Cannot go out	1.75	1.27, 2.42	<0.001	2.09	1.59, 2.74	0.000	1.73	1.19, 2.49	0.004
Feeling the responsibility of needing to provide care and experiencing anxiety	1.77	1.31, 2.40	<0.001	2.25	1.76, 2.88	0.000	1.98	1.40, 2.79	0.000
Feeling depressed	1.83	1.34, 2.50	<0.001	1.88	1.46, 2.42	0.000	1.73	1.22, 2.47	0.002
Feeling easily fatigued	2.12	1.55, 2.89	<0.001	2.13	1.66, 2.74	0.000	1.92	1.35, 2.73	0.000
Being unable to concentrate on work or hobbies and pleasure	2.19	1.59, 3.01	<0.001	1.92	1.48, 2.47	0.000	1.75	1.23, 2.50	0.002
Feeling anxiety about life in the future	1.59	1.18, 2.14	0.002	2.14	1.69, 2.72	0.000	2.26	1.61, 3.17	0.000
Unable to have enough time for yourself	1.96	1.44, 2.66	<0.001	1.83	1.43, 2.34	0.000	1.53	1.09, 2.17	0.015
Feeling like care giving is worsening your physical condition	2.01	1.39, 2.90	<0.001	1.90	1.42, 2.55	0.000	1.70	1.20, 2.31	0.012

OR: odds ratio, 95% CI: 95% confidence interval.

^a Adjusted for age of patient, age of caregivers, time since first diagnosis, relationship to patient, and Hoehn and Yahr stage.

variations in the exact rate of occurrence depending on the examination methods used, EMO has a higher rate of occurrence in patients with PD. This study has confirmed that this is the same for patients with early stage PD. Moreover, approximately 70% of caregivers answered that they have dealt with EMO, and many caregivers are aware of EMO. On the other hand, the caregivers' responses that indicated they have dealt with EMO were approximately 10% less than the patients' responses. Thus, it is essential to consider that the percentage of patients who are self-conscious of EMO exceeds the percentage of caregivers who objectively observe EMO. In the research conducted by Stacy et al. on patients with PD who have had the disease for <5 years, the percentage of wearing-off that could be detected from interviews was 29.4%. However, when using a self-administered patient questionnaire known as the Wearing-off Questionnaire (WOQ), wearing-off was detected at a rate of 57.1%. Thus, this research describes the necessity of tools to accurately grasp the patient's subjective symptoms [9].

One problem that is caused by EMO is the appearance of dystonia that occurs when the concentration of anti-Parkinson's drugs in the serum is reduced. This is painful and can cause sleep disorders, and is known to be an issue that requires caregiver attention [10,11]. In this study, however, only approximately 10% of respondents answered that they "woke up due to pain" as a result of EMO. Nevertheless, the percentages of people who answered that EMO caused "difficulties changing clothes," "difficulties using the bathroom," and "being unable to be active in the morning" was quite high; thus, it became apparent that patients felt that EMO was a problem that impacted activities of daily living (ADL) more than it caused a sleep disorder. There was a higher percentage of patients in the early stages of PD who responded that they were "unable to be active in the morning" similar to patients in advanced stages, and the impact that this has on social activities like work and housework is consequently a problem. Moreover, this survey showed that the PDQ-8-SI scores were higher for the group of patients with EMO than they were for the group without EMO; this demonstrates that EMO has an impact on the patients' QOL. We found only a correlation between EMO and the dopamine agonist (DA) usage from the patient answers (rate of DA usage: with EMO, 63.8%; without EMO, 58.0%; $p = 0.045$). When considering EMO with patient's level of severity, the group with EMO had a significantly worse QOL for people in stages I–IV on the Hoehn and Yahr scale. Chapuis et al. have identified the impact of early-morning akinesia on QOL [7]. Factors that have been reported to lower the QOL of patients with PD are the level of severity on the Hoehn and Yahr stage [11], unified Parkinson's disease rating scale (UPDRS) score [12], longer disease duration [13, 14], and presence of depression as a complication [15,18–20]. In addition, Rizos et al. demonstrated that EMO was also associated with significant non-motor off symptoms including urinary urgency, anxiety, dribbling of saliva, pain, low mood, limb paresthesia, and dizziness in 88% of patients [21]. We calculated the odds ratio to confirm the correlation of EMO with the presence of depression. We found a correlation

between EMO and the presence of depression (OR: 2.027, 95% CI: 1.600–2.568, $p < 0.001$).

Moreover, EMO is also believed to be a cause of deterioration of the patient's QOL, and it is necessary to gather appropriate information regarding it and to provide treatment intervention. In recent years, long-acting dopamine agonists have been released in the market, and it has been reported that these improve nighttime sleep disorders and early morning motor symptoms [16]. This is believed to be one of the potential treatment options.

This survey clarifies that EMO increases the burden on caregivers. There are several reports concerning the factors that cause an increase in the burden on caregivers. Carter et al. have reported that as the level of severity of PD increases, the burden placed on the caregivers increase and the health of the caregivers themselves is threatened [17]. Pal et al. have reported that the duration that the patient has had the disease, presence of depression, and decline in cognitive function are all factors that increase the burden on the caregiver and the possibility that the caregiver will also become depressed [18]. In this study as well, the odds ratio for the caregiver burden for all of these items increased from approximately 1.6–2 when comparing the patients at stage III or higher with those at stages lower than stage III. Accordingly, the patient's level of severity is suggested to be a factor that makes caregiver burden worse. To remove the influence of age of patient, age of caregivers, disease duration, relationship to patient, and Hoehn and Yahr stage, an adjusted odds ratio was calculated using the multivariate logistic regression analysis. Even with this adjusted odds ratio, EMO significantly increased the caregiver burden; therefore, it is believed that EMO causes an impact on caregiver burden independent of the patient's level of severity. As PD progresses, the role of the caregiver becomes more important. In this survey, spouses accounted for approximately 80% of caregivers, and the average age of the caregivers was 67.7 years. This clearly shows that in the current survey, most caregivers are also aged. Many caregivers suffer from depressive tendencies due to the anxiety associated with providing care with an uncertain future. Peters et al. have reported that while the physical health of caregivers for people with PD is not different from the average population of the same age range, their emotional health is lower than the average population [19]. There is a correlation between caregiver burden, depression, and QOL [20], and it is essential for long-term treatment strategies of PD to take into consideration not only the QOL of patient but also the emotional health and QOL of the caregiver. Therefore, strategies must be implemented to reduce caregiver burden.

5. Conclusion

The results of this survey have revealed that EMO is highly prevalent according to both patients and caregivers. EMO affects the patient's ADL, and it lowers their QOL. Moreover, since this could cause an increase in caregiver burden, consideration for caregiver burden should be taken

during medical intervention and appropriate gathering of information as necessary.

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